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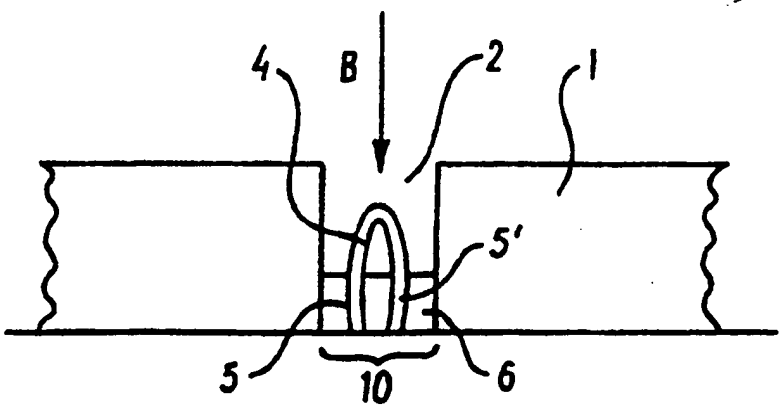
(54) Title: MICRO-FILTRATION DEVICE

(57) Abstract

There is described a filter unit (10) which comprises a hollow fibre membrane fixed into a solid plug (6) and able to communicate with each side of the plug (6). Utilisation of the hollow fibre membrane enables a relatively large filtration area to be exposed to the sample, thus facilitating filtration. For example, the hollow fibre membranes may be in the shape of hoops (4), having their ends (5, 5') passing through the plug (6) and exposed on the far side thereof. The plug (6) is desirably formed from cured adhesive. The filter unit (10) may be located in each well (2) of a conventional filter tray (1) or may be located in the lumen of a filtration apparatus such as a pipette (11). Optionally the membrane may be treated or coated to react with a component of the sample.



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"Micro-filtration Device"

The present invention is concerned with the process of filtration, particularly micro-filtration, and provides a device capable of small volume filtration.

Filtration is a common separation technique of samples and is frequently used in both chemical and biochemical processes. In particular, filtration is of utility for biological samples where cell debris and other organic materials need to be removed. For this reason, many medical diagnostic assays require a first filtration step.

Generally dead-end filtration is used, in which the sample is induced to pass through the filter by a pressure differential, a portion of the sample being retained on the filter and the remaining part of the sample (the filtrate) passing through the filter and being collected in a suitable chamber.

Filters may also be used as a convenient matrix on which to present samples for assay purposes.

There is an increasing trend to use smaller volume

samples for filtration and where this is the case it is usual to use a scaled-down filtration apparatus as appropriate.

In such small volume filtration procedures, filtration trays or pipettes are generally used. Filtration trays consist of multiple open-ended wells positioned on top of a single sheet of filter paper. The area of each well therefore defines the area of filter available for the filtering operation as the surface area of the filter available for each filtration process is limited to the surface area of the membrane as exposed by the well. Each well can be used to filter a separate sample and the whole tray can therefore be used in multiple filtration operations. Typically, such filtration trays consist of 24, 48 or 96 separate wells, each well ending with the membrane as the lower surface.

Figure 1A illustrates a cross-section of a single well in a portion of a conventional micro-titre tray adapted for normal use for micro-filtration processes. The tray (1) contains numerous filter chambers (2) into which the sample(s) are placed for filtration. Prior to filtration a filter paper (3), which is essentially flat, is fixed firmly to the exterior bottom surface of the filtration tray (1). Once the filter paper (3) is in position the sample to be filtered is poured into the filter chamber (2). Optionally pressure in the direction of arrow A is applied. The pressure forces the sample through the filter paper (3) into a collection chamber (not shown). It is clear from Figure 1A that the surface area available for filtration is limited to the cross-sectional area of the filter chamber (2).

However, wh re the surface area of the filter is small the filtration operation tends to suffer from the following disadvantages:

1. The process of filtration may take a long time as the sample has to pass through a relatively small surface area of filter.

2. If biological samples are to be filtered the relatively small surface area of the filter is highly prone to being completely clogged with cell debris, fatty deposits or other impurities.

An alternative conventional filtration operation occurs using a pipette, in which a planar filter is located within or on the tip of the pipette. The liquid sample is taken up into the pipette by suction and is filtered. A portion of the sample may be retained on the filter whilst the filtrate is collected within the body of the pipette. Optionally, the tip of the pipette having the filter may be removable (and/or optionally disposable) so that the used filter (and any contaminant contained thereon) can be removed before expulsion of the filtrate. The filter may be treated or coated to react with or bind to a particular component of the sample. An example of a pipette tip having a treated membrane located thereon is the Nuclitips™ DNA extraction system of Amersham Life Sciences Ltd. In the Nuclitips™ pipette tip a planar treated membrane is located on the exterior of the pipette tip totally covering the tip's aperture, so that the sample is filtered before entry into the pipette tip and any DNA present in the sample binds to the filter.

The present invention provides a filter unit comprising

a hollow fibre membrane fixed into a solid plug.

Viewed from another aspect the present invention provid s a membrane for a filter unit in which the membrane has a greater filtration surface area than the cross-sectional filtration area of the filter chamber. Generally the membrane is essentially three-dimensional. The membrane may have any convenient shape or configuration.

The term "cross-sectional filtration area" refers to the area of a cross-section of the filter chamber over which filtration occurs. Normally this would be the area of the floor of the filter chamber or the internal diameter of a pipette lumen tip. It may be possible to locate the filter part way along the length of the filter chamber. If the walls of the filter chamber are sloping (and therefore the cross-sectional area of the filter chamber varies) the "cross-sectional filtration area" is the cross-sectional area of the filter chamber at the point where the filter is located.

The membrane according to the present invention is fixed into a solid plug and the plug is adapted to form a tight fit with the internal walls of the filter chamber of interest.

It is important that part of the filter according to the invention communicates with the exterior sides of the plug so that the sample placed into the filter chamber (and optionally subjected to pressure to urge the sample across the filter) can be separated, the filtrate being collected in a collection chamber placed below the filtration apparatus.

In one embodiment the filter of the present invention

is formed from hollow fibre membranes which are wound round to form a spiral. The spiral may be either two dimensional, that is forms a flat coil, or may be three-dimensional in which case the spiral is wound upwardly into a apex.

In an alternative embodiment the filter is formed from "U"-shaped hoops of hollow membrane fibres. Preferably several hoops, for example over 10 hoops, especially 20 to 50 hoops, are present in each filter chamber.

In a yet further embodiment the filter is formed into hoops as described above, but the upper portion of the hoops are bent into an acute angle, thus forming an inverted "V" shape. The angle may conveniently be introduced into the membrane by spot application of heat which welds the sides of the membrane together at the point where heat is applied, thus forming a hinge.

In another embodiment, hollow fibre membranes each having a "blind" or closed end may be used. In one arrangement the blind ends may be exposed to the sample. For example, multiple short lengths of hollow fibres may be used, the blind end of each fibre being exposed to the sample whilst the open ends are potted into the plug and communicate with the filtrate chamber. Conveniently the blind ended fibres diverge away from a central portion of the plug into which the fibres have been potted.

In an alternative embodiment using blind ended hollow fibre membranes, short lengths of the fibres are cut and joined together at the apex (thus closing their lumens at that point) into a "teepee"-like shape. The apex is exposed to the sample whilst the opposite ends of the membrane fibres pass through the plug and are

exposed on the opposite side thereof.

The filter of the present invention is located within the filter chamber by means of the plug. The plug forms a tight fit with the inside surfaces of the filter chamber. It is essential that the plug and filter chamber walls form a seal, as the sample to be filtered could otherwise pass through the gap between the plug and the interior of the filter chamber. The filter itself is at least partially embedded within the plug.

The plug will normally be formed from adhesive, usually cured adhesive. Any material capable of forming a seal with the membrane fibres and the filter chamber may be used.

The adhesive used to form the filter plug of the present invention may be any adhesive material which does not react with the membrane or filter chamber materials in a deleterious manner. Preferably the adhesive material is quick setting, ie cures within minutes, for example under 5 minutes. For certain embodiments adhesive material which cures upon exposure to light is particularly desirable. For example in medical applications it may be preferred to use adhesive which cures upon exposure to blue light, especially UV light.

Suitable adhesive material is commercially available and mention may be made of polymers available from Ablestick Ltd (for example LCM 32, LCM 34 and LCM 35), Bostick Ltd or Dynax Inc (eg 191M) as being suitable UV curing adhesives.

In the invention it is essential that one portion of

the membrane is exposed to the unfiltered sample and that another portion of the membrane communicates with the collection chamber. For example, where the filter is a two-dimensional spiral, the spiral will be fixed into the plane of the plug, with one surface facing the filter chamber and the other surface facing the collection chamber. In this embodiment the filtrate must undergo two filtering operations, firstly across the membrane into the lumen of the hollow fibre and secondly from the lumen to the collection chamber side of the filter. Where the filter is in a hoop-like or inverted "V" configuration, the ends of the hoop or inverted "V" are located within the plug and pass through the plug so that the lumen of the cut ends of the hollow fibre membrane are exposed to the collection chamber side of the filter apparatus. In this embodiment the sample passes through the hoop or inverted "V" part of the filter into the lumen thereof and runs down to the ends of the lumen and out into the collection chamber.

Viewed from one aspect the present invention comprises a filtration device having at least one filter chamber containing a hollow fibre filter potted into a solid plug. The surface area of the filter is desirably greater than the cross-sectional area of the filter chamber floor.

Conveniently the filtration apparatus comprises multiple filter chambers, each having an individual filter. For example, the apparatus of the invention may be a tray of any suitable material (for example plastics), having multiple wells therein (eg. 24, 48 or 96 wells), each well being capable of being a filter chamber. Alternatively, the apparatus may be in the form of a pipette or a pipette tip. The filter unit is

sealed into the lumen of the pipette or pipette tip creating an internal volume within the pipette or tip which may only be accessed by the sample passing across the filter. The internal volume so formed acts as the filtration chamber. Following filtration of the sample, the pipette tip containing the filter unit may be removed, for example may be snapped off, and the filtered sample may be simply expelled from the pipette. Alternatively, filtrate may be expelled via an alternative opening in the device or may be expelled back through the original opening, passing through the filter again. The pipette embodiment may also be used to detect the presence of a component with the sample, the component binds to the filter and is then detected. The filtrate is a by-product in this embodiment. Again the portion of the pipette or tip containing the filter and the component of interest may be removable as described above, facilitating measurement, detection or further reaction thereof.

For convenience, the filter chamber and, optionally, the plug as well are transparent or translucent being formed from optically clear materials to enable monitoring of filtration and/or the output from any assay that can be measured by optical means.

The present invention also provides a process for separating a sample by filtration, in which the sample is passed through a filter as described above.

The membrane material may be any suitable membrane, and selection of the membrane type will depend upon the filtering process in question. Examples of suitable membrane materials include polysulfone, cellulose, cellulose diacetate and/or polypropylene. Nylon filter membranes, cellulose nitrate, polytetrafluoroethyl ne

(PTFE), polyvinylidene difluoride (PVDF) and glass fibres can also be used.

A wide variety of such membranes are commercially available and can be bought with a range of pore sizes so that selection of the filter to suit the sample can be made.

The membrane is in the form of a hollow fibre and desirably the internal diameter of the hollow fibre is small, for example is under 2mm, especially is under 1mm. The internal diameter of the hollow fibre may be 500μm or less, for example 300μm or less.

To produce the filters according to the present invention a bundle of hollow fibre membranes are taken. The bundle may contain any convenient number of membrane fibres, but normally will contain from 5 to 50 membrane fibres, for example 10 to 20 membrane fibres. For example, to produce the "teepee" type of arrangement the bundle of membrane fibres is welded by a spot application of heat at intervals along the membrane bundle. Approximately equi-distant from two welds an adhesive plug is formed using adhesive, preferably quick-setting adhesive, and mention may be made of LCM 32 and LCM 35 of Ablestick Ltd. Optionally the plug shape is predetermined either by fitting a collar around the membrane bundle (and the collar may be fitted either before or after the welding operation has taken place) or by placing the membrane bundle into a suitable mould and injecting the adhesive to fill the available space. Once the adhesive is set the plug is chopped in half transversely, for example using a scalpel, razor blade or guillotine. Thus two plugs are formed, into each of which the lumen of each membrane fibre is flush with the newly created plug

surface. At this stage in th procedure there is obtain d a shorten d membrane bundle having an adhesive plug at each nd, and approximately in the centre thereof a point where the membrane fibres are welded together. The weld is then cut in half and two filters according to the present invention are formed. The weld may be cut by use of a scalpel, guillotine or razor blade.

It is also possible to modify the process so that the welds are cut before the adhesive plug is cut in half or even before formation of the adhesive plug. Each filter formed by this process is then inserted into a filter chamber by press-fitting the plug into the aperture of the filter chamber. The adhesive plug and the inside walls of the filter chamber form a tight fit.

To form the hoop or "V" shaped filter the membrane fibre bundle is first bent into a "U" shape, for example bending the membrane bundle around a suitable forming rod. An adhesive plug is then formed in a similar manner as that described above, namely either by insertion of the "U" shaped membrane bundle into a suitable mould or by fitting a collar around the bundle and then filling the collar or the mould with adhesive, followed by curing, if necessary. The inverted "V" shaped filter is formed from the hoop-shaped filter and comprises the additional step of spot welding the hoop at the apex so that a sharp corner is formed where the heat is applied. The inverted "V" shaped filter is preferable in some circumstances since this configuration may be easier to insert into the filter chamber.

Alternatively, the hoop or inv rted "V"-shaped filter

may be produced by forming a shortened membrane bundle with an adhesive plug at each end as described above. The shorten d membrane bundle may then be formed into a "U"-shape and the plugs affixed together side-by-side (for example by glueing) to give the required plug shape. For the "V"-shaped embodiment application of the heat to create the acute angle required may occur either before or after the plug ends are glued together to form the final plug required.

For the purpose of simple "dead-end" filtration the filtration chamber will normally be located substantially vertically. However, it is equally possible for the filters to be used in a filtration device which is arranged away from the vertical. In such an embodiment it may be necessary for pressure means (such as a pump, especially a suction pump) to be provided in order to filter the sample.

The filters of the present invention are equally applicable for a "cross-flow" filtration apparatus and still provide the advantages obtained by presenting a relatively large surface area in a small filtration chamber.

The filters of the present application are also of use as a matrix on which to present a test substance for assay. The relatively large surface area of the filter enables a concentration of the test substance and thus amplification of the test result is possible.

The present invention will now be described with reference to the drawings in which Figs. 1B to 7 show configurations of the membrane within the unit and Figs. 8 and 9 show one use of the unit in a pipette tip. In more detail:

Fig. 1A illustrates a conventional filtration tray 1 with well 2 and filter pap r 3 as discussed above.

Figure 1B illustrates a single well in a portion of a filtration apparatus in the form of a filtration tray having a filter of the present invention embedded in a plug as described above. Figure 1B illustrates a cross-section of a portion of a filtration tray 1. A filter chamber 2 is illustrated and contains at the bottom thereof a filter unit 10 according to the invention. Unit 10 consists of a solid plug 6 which forms a tight fit with the internal walls of the lumen of the filter chamber 2. The plug 6 may be located in the filter chamber 2 either by virtue of the resilient nature of the plug 6 itself or by application of adhesive between the plug 6 and the inside walls of the filter chamber 2. A hollow fibre membrane is shown in the form of a hoop 4, the ends 5,5' of the hoop 4 being held within plug 6. For simplicity only one hoop 4 is illustrated in Figure 1B although generally several such hoops which may be the same, similar or of varying sizes may be present each having their ends 5,5' located in plug 6.

Figure 2A shows a schematic cross-section of a filter unit 10 according to the present invention. The unit 10 illustrated in Figure 2A has a membrane in a spiral configuration being either the two-dimensional coil or alternatively the lower coil of the three-dimensional spiral as shown in Figure 5. As illustrated in Figure 2A the plug 6 forms a tight fit with the internal walls 1,1' of the filter chamber 2. There is no gap between the sides 1,1' of the filter chamber 2 and plug 6. Embedded within the plug 6 is a membrane in the form of a hollow fibre. The upper surface 8 of the hollow fibre is xpos d to the untreated sample which is added

into filter chamber 2. The lower surface 9 of the hollow fibre is exposed from plug 6 and permits the filtrate to pass through into the collection or filtrate chamber (not shown).

In use a liquid sample is inserted into filter chamber 2. Selective filtration of the sample occurs with the filtrate passing through the upper surface 8 of the membrane fibre into the lumen 7 thereof. From lumen 7 the filtrate passes through the lower surface 9 of the hollow fibre into a collection or filtrate chamber (not shown). Optionally a downwardly pressure is applied either by a positive pressure onto the sample in the filter chamber 2 or a negative pressure from the filtrate collection side, to draw the filtrate through the filter unit 10.

Figure 2B illustrates an embodiment of the invention when the filter unit 10 has a membrane arranged in the configuration of a hoop. Again, plug 6 forms a tight fit with the internal walls 1,1' of filter chamber 2. In this embodiment the hollow fibre membrane is positioned with its free ends 5,5' exposed on the filtrate collection side of plug 6, with the main body of the membrane being present in the filter chamber 2. The dotted lines extend the hollow fibre upwardly into the filter chamber 2 but are not drawn to scale. It is also possible that instead of the filter being bent into a hoop as illustrated in Figure 2B the two strands come together into an apex in which the sides of the fibre are spot welded together through the application of heat or adhesive. In use the liquid sample is placed into a filter chamber 2 and separation of the sample takes place as components of the sample migrate through the surface of the membrane into the lumen 7 of the hollow fibre. The filtrate pr sent in lumen 7

travels down the hollow fibre membrane and is collected from the free ends 5,5' beneath which is located a collection vessel (not shown).

In Figure 2B the free ends 5,5' of the hollow fibre membrane are shown passing through plug 6 and protruding therefrom. It is also possible for these ends 5,5' to be flush with the lower surface of plug 6 and indeed for ease of manufacture of the filter unit 10 this configuration may be preferable.

Figure 3A is a top view of a membrane for a filter unit according to the present invention, in the form of a two-dimensional spiral. Figure 3B illustrates the side view of the same membrane. The spirally arranged membrane shown in Figures 3A and 3B is embedded within a plug (not shown) to form a filter unit.

Figure 4 is a perspective view of a membrane for a filter unit according to a further embodiment of the present invention, the membrane being formed of short strands of membrane fibres affixed together at the apex into a "teepee" arrangement. The lower ends of each membrane strand are embedded within a plug (not shown) so that the lumen of each strand is free to discharge filtrate into a collection chamber (not shown).

Figure 5A is a side view of a further embodiment of a membrane according to the present invention in the form of a three-dimensional spiral filter, with Figure 5B illustrating the top view of the same membrane filter. The lower portion of the spiral is embedded within a plug (not shown) so that the lower end of the filter is exposed on the filtrate collection side of the plug.

Figure 6 is a schematic representation of a filter unit

10 according to the present invention having a plug 6 through which the hollow fibre membrane strands are each formed in the shape of a hoop 4. Multiple hoops 4 are present, each having their ends passing through an adhesive plug 6, the lumen of each membrane strand being exposed on the lower surface of the plug 6. In Figure 6 four membrane fibre hoops 4 are illustrated for the purpose of simplicity but it is also possible for many more hoops to be present in each plug 6, for example up to 20 hoops. The hoops may either be of the same or similar size as illustrated in Figure 6 or may be of varying sizes, that is to say the height of the hoop 4 may vary. Within one preferred embodiment each filter unit 10 is composed of sets of hoops 4, each hoop 4 set being of different size. It is also possible for the axis of each set of hoops to be located in a different directions within the plug relative to each other.

Figure 7 illustrates schematically a further embodiment of the invention in which the filter unit 10 is formed from hollow fibre membranes in the configuration of an inverted "V". Again, Figure 7 only shows four such strands 4' for purposes of simplicity but it may be possible to have far more strands present on each plug 6.

Figure 8B illustrates device 11 incorporating a filter unit 10 according to the invention. The filter unit 10 is sealed into an interior lumen of device 11, here illustrated as a disposable pipette tip. The filter unit 10 shown comprises plug 6 incorporating therein hoops 4 of hollow fibre membrane. However, any alternative filter unit 10 described above would also be suitable for use in device 11.

In us a liquid sampl nters through aperture 15 driven upwardly in the direction of the arrow by the suction pressure created within the pipette apparatus (shown generally in Fig. 8A). The filtrate passes through the filter unit 10 as previously described into the collection area 14. Optionally, components of the filtrate may be localised on the upper hydrophobic membrane 12 but normally hydrophobic membrane 12 is used to repel the liquid sample, which may for example of an aqueous nature. The filtrate is therefore prevented from entry into chamber 16 and is instead retained within collection area 14.

In the pipette embodiment illustrated in Figure 8B a snap point 13 is shown which enables the lower portion 17 of the pipette tip to be detached from the upper portion 18. Portion 17 of the tip 11 may then be disposed of in situations where the components of interest are located on hydrophobic membrane 12 or where the filtrate sample of interest is retained within storage area 14 the filtered sample can be simply poured into a further vessel for easy handling and/or further processing.

In a yet further embodiment the filter unit 10 may retain the component of interest on the hollow fibre membrane strands. The filtrate in this embodiment may be of no interest and, following removal of portion 17 by cleavage at snap point 13, the filtrate collected in storage area 14 may be thrown away and the filter unit carefully washed to remove the bound sample of interest located on the hollow fibre membrane.

Figure 8C illustrates an alternative device 11 also containing a filter unit 10 as described above in Figure 8B. Hydrophobic membrane 12 is also

illustrated.

The device shown in Figure 8C comprises a non-return valve 19 immediately above filter unit 10. Thus, filtration of a liquid sample causes the filtrate to collect in storage area 14 which is bounded by hydrophobic membrane 12 and the non-return valve 19 immediately above filter unit 10. To expel the filtrate, positive pressure is exerted by means of the pipette apparatus illustrated in Figure 8A, and this causes the filtrate to be expelled through aperture 22 of arm 20 which optionally contains a non-return valve 21.

Figure 9 illustrates an alternative device 11 containing a filter unit 10 according to the invention. Filter unit 10 comprises plug 6 and hoops 4 of hollow membrane fibres. Only 3 hoops are illustrated in the unit 10 as shown for the purposes of simplicity. The number and size of the hoops 4 may vary as required. Likewise, it is possible to alter the configuration of the membranes within the filter unit as required. In device 11 as illustrated a primary membrane 23 covers the aperture of the pipette tip. The primary membrane 23 serves to exclude course matter from the liquid sample admitted into the lumen of the pipette tip, thus avoiding clogging of the hollow fibre membranes by large particulate matter. In the device illustrated hydrophobic membrane 12 is located immediately above snap point 13 and the device operates in a similar manner to that described in Figure 8B.

CLAIMS

1. A filter unit comprising a hollow fibre membrane fixed into a solid plug and able to communicate with each side thereof.

2. A filter unit as claimed in Claim 1 wherein the membrane has a greater filtration surface area than the cross-sectional area of the plug.

3. A filter unit as claimed in either one of Claims 1 and 2 wherein said membrane is non-planar.

4. A filter unit as claimed in any one of Claims 1 to 3 wherein said plug is adapted to form a tight fit with the internal walls of a filter chamber.

5. A filter unit as claimed in any one of Claims 1 to 4 wherein said plug is transparent or translucent.

6. A filter unit as claimed in any one of Claims 1 to 5 wherein said plug is formed from adhesive.

7. A filter unit as claimed in Claim 6 wherein said plug is formed from UV or light curable adhesive.

8. A filter unit as claimed in any one of Claims 1 to 7 wherein said membrane is selected from polysulphone, cellulose, cellulose diacetate, polypropylene, nylon, cellulose nitrate, polytetrafluoroethylene, polyvinylidene difluoride and/or glass fibres.

9. A filter unit as claimed in any one of Claims 1 to 8 wherein the internal diameter of the hollow fiber membrane is less than 2mm.

10. A filter unit as claimed in Claim 9 wherein the internal diameter of the hollow fibre membrane is 500μm or less.

11. A filter unit as claimed in any one of Claims 1 to 10 having a single hollow fibre membrane wound into a spiral configuration.

12. A filter unit as claimed in any one of Claims 1 to 11 having a hoop shaped hollow fibre membrane, both ends of which pass through the plug and are exposed on one side thereof.

13. A filter unit as claimed in Claim 12 having 20 or more such hoops located in said plug.

14. A filter unit as claimed in any one of Claims 1 to 10 having a blind ended length of hollow fibre membrane, the blind end being exposed to the sample.

15. A filter unit as claimed in Claim 14 wherein the blind ends diverge from each other.

16. A filter unit as claimed in any one of Claims 1 to 15 having a treated or coated membrane.

17. A device having a filter unit as claimed in any one of Claims 1 to 16 located therein.

18. A device as claimed in Claim 17 wherein the portion of said device containing said unit is separable from the remainder of the device.

19. A device as claimed in either one of Claims 17 and 18 having a non-return valve located between said

filter unit and a collection chamber for the filtrate.

20. A device as claimed in any one of Claims 17 to 19 having an aperture dedicated to expelling the filtrate.

21. A device as claimed in any one of Claims 17 to 20 having multiple filter units according to any one of Claims 1 to 16.

22. A process of forming a filter unit as claimed in any one of Claims 1 to 16, said process comprising the following steps:

a. obtaining a membrane in the form of hollow fibre(s), optionally cutting said fibre(s) to the required size and/or conforming said fibre(s) to the required shape;

b. forming a solid plug at a required location around said fibre(s); and

c. optionally trimming the ends of the fibre(s).

23. A process as claimed in Claim 22 wherein the hollow fibre(s) are treated to produce a blind end at one end thereof.

24. A process of filtering a sample, said process comprising passing said sample through a filter unit as claimed in any one of Claims 1 to 16

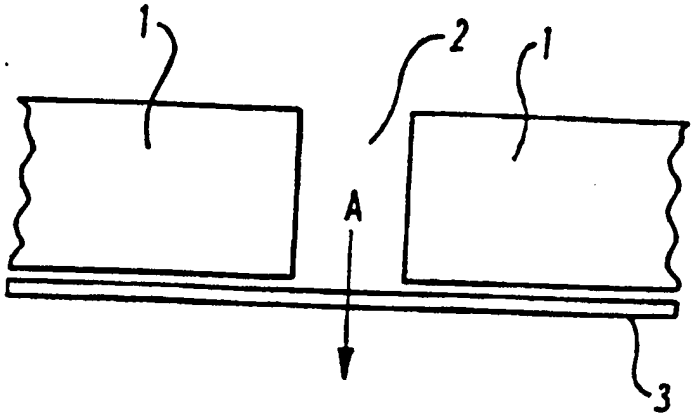

FIG.1A

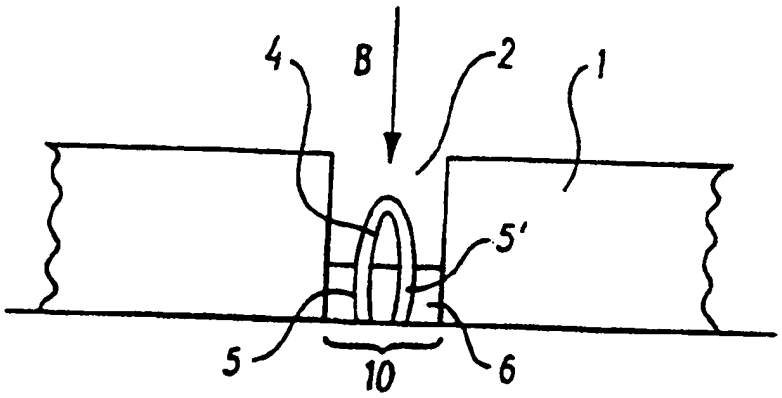

FIG.1B

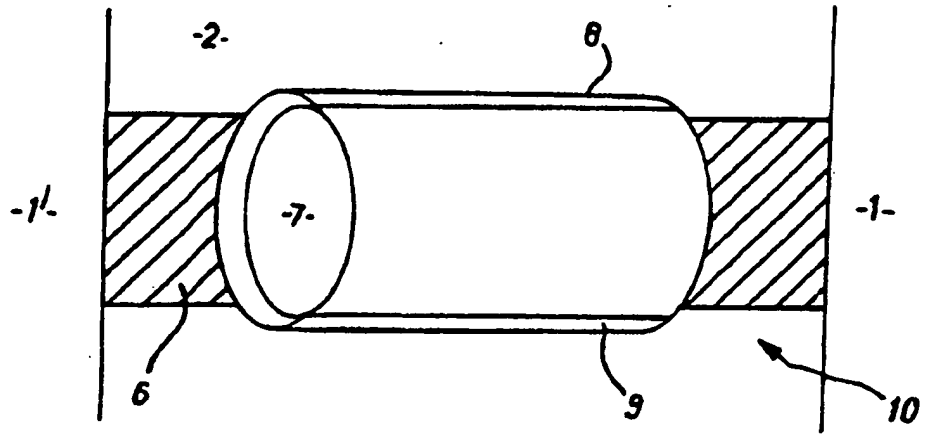

FIG.2A

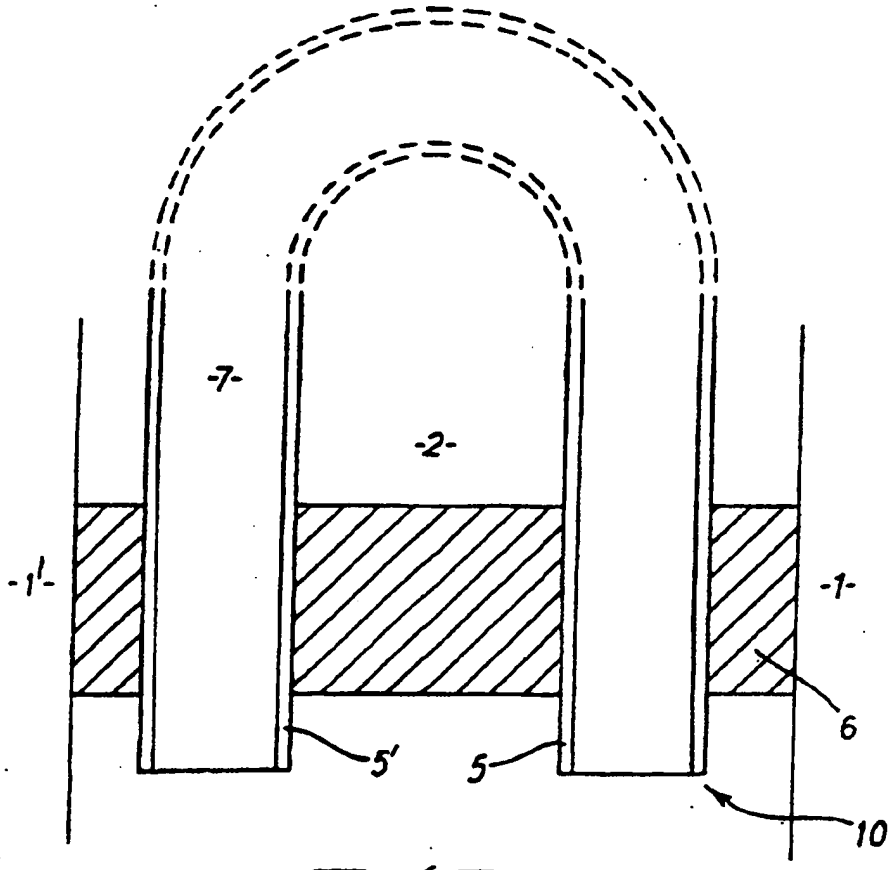

FIG.2B

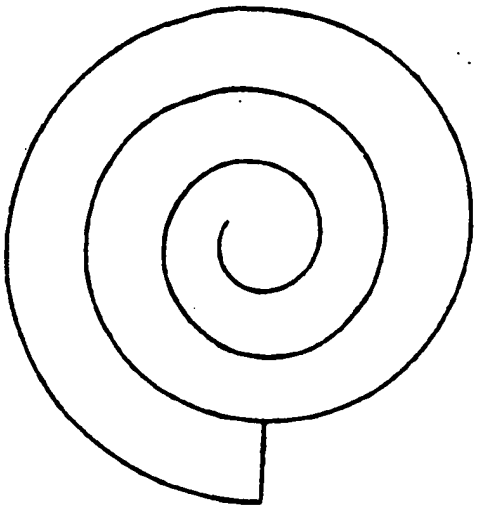

FIG.3A

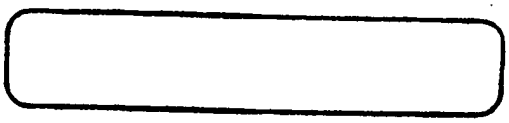

FIG.3B

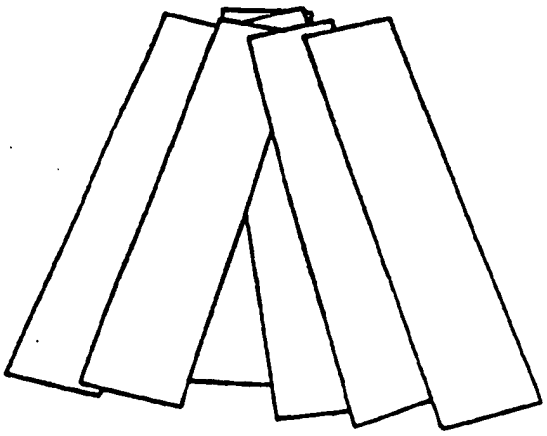

FIG.4

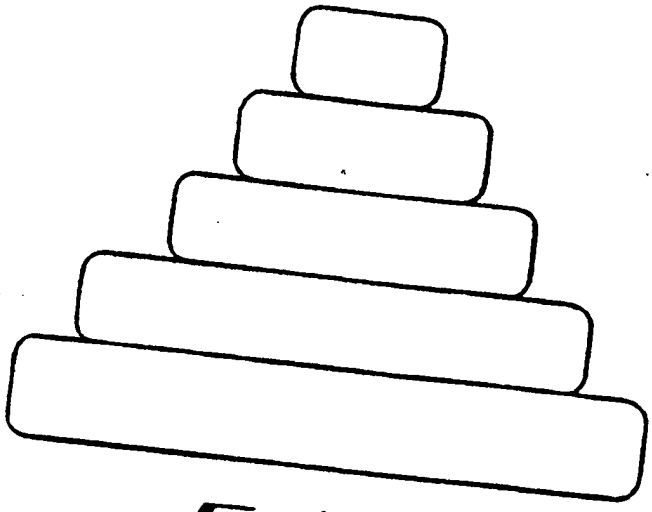

FIG.5A

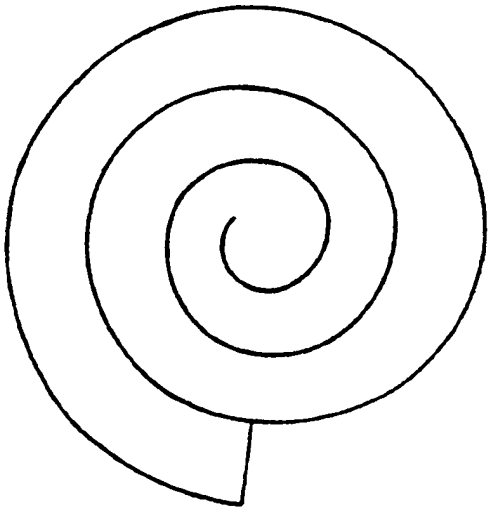

FIG.5B

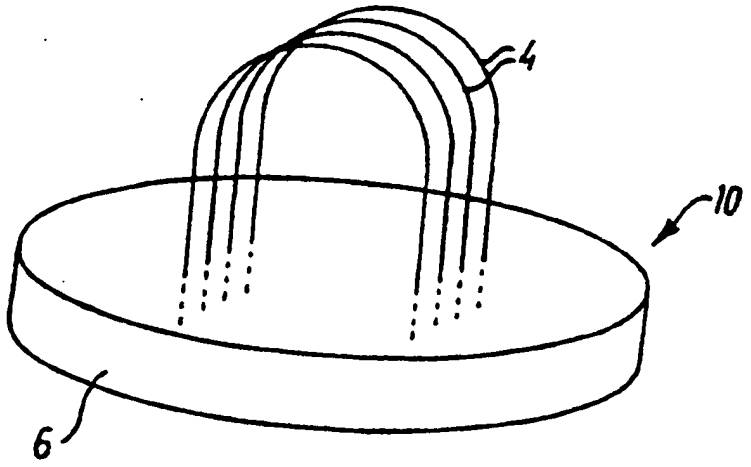

FIG 6

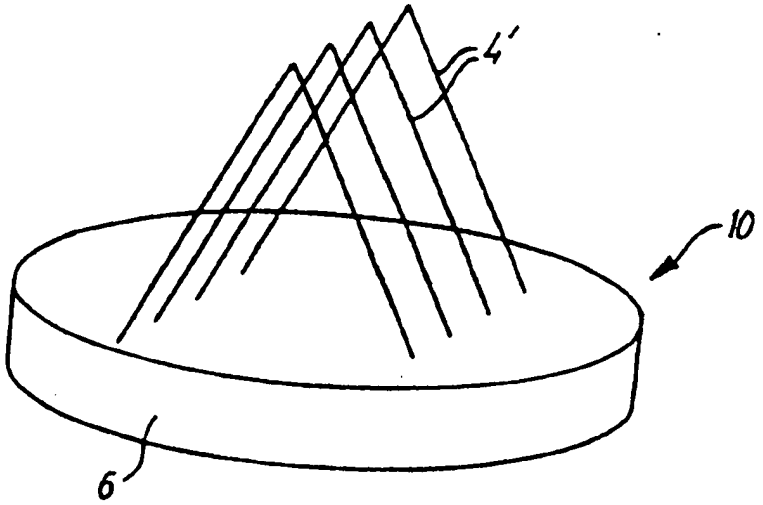

FIG. 7

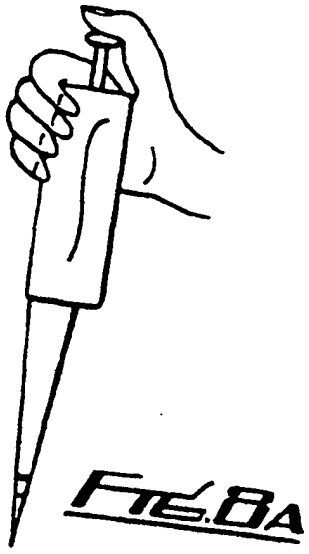

FIG. 8A

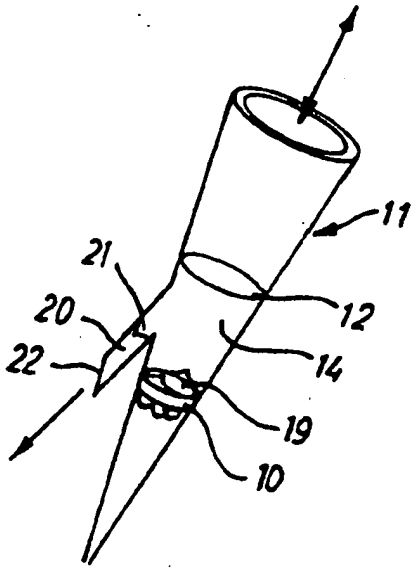

FIG. 8C

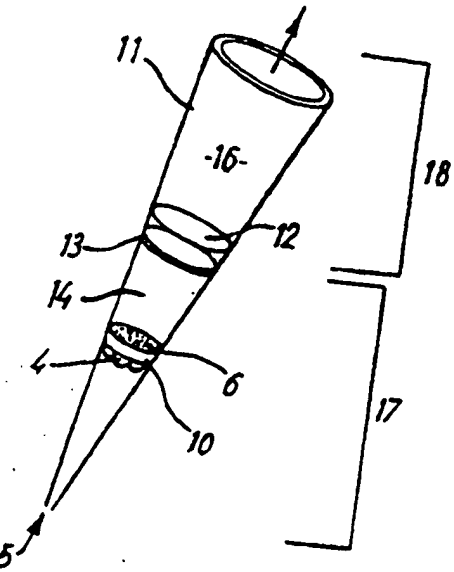

FIG. 8B

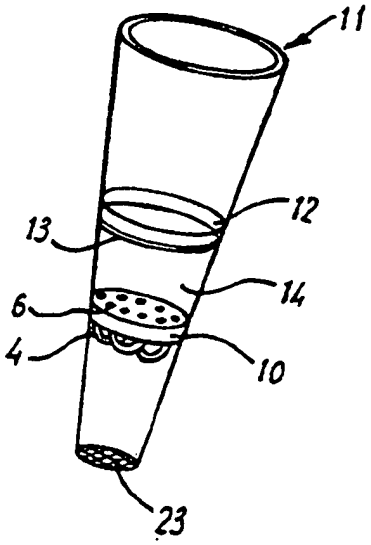

FIG. 9

INTERNATIONAL SEARCH REPORT

Inter onal Application No
PCT/GB 95/02834

A. CLASSIFICATION F SUBJECT MATTER
IPC 6 B01D63/02 B01D61/18 B01L3/00 G01N1/40

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 B01D B01L G01N

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PATENT ABSTRACTS OF JAPAN vol. 12 no. 344 (C-528) ,16 September 1988 & JP,A,63 104615 (ASAHI CHEM IND CO LTD) 10 May 1988, see abstract	1-4,6,8, 9,12-14, 17,20, 22-24
A	& DATABASE WPI Section Ch, Week 8824 Derwent Publications Ltd., London, GB; Class A88, AN 88-165566 see abstract	5,7,10, 15,16,21
X	GB,A,2 173 711 (TOYO SODA MFG CO LTD) 22 October 1986 see the whole document	1-4,6,8, 9,14,17, 24

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
10 April 1996	26 -04- 1996

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Hoornaert, P

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INTERNATIONAL SEARCH REPORT

Intern nal Application No
PCT/GB 95/02834

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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X	US,A,5 228 992 (DEGEN) 20 July 1993 see the whole document	1-4,6,8, 9,12,13, 22
X	FR,A,2 393 662 (CORDIS DOW CORP) 5 January 1979 see claims 1,2,6,7; figures 2-4 see page 7, line 28 - page 8, line 1 see page 10, line 23 - page 11, line 18	22
A	PATENT ABSTRACTS OF JAPAN vol. 17 no. 258 (P-1540) ,20 May 1993 & JP,A,05 002021 (KONICA CORP) 8 January 1993, see abstract & DATABASE WPI Section Ch, Week 9306 Derwent Publications Ltd., London, GB; Class B04, AN 93-049943 see abstract	1-4,8,17

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr ...al Application No
PCT/GB 95/02834

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